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modification, wherein said 2' modification comprises the formula (O-CH₂-CH₂)_n-O-alkyl, and a heteroatomic backbone modification, wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof.

REMARKS

After entry of the above amendment, claims 27-29, and 34 will be pending in this patent application. The specification has been amended to recite the claim of priority. An executed substitute declaration will be submitted in due course. Claim 33 is canceled herein, without prejudice. Claims 27 and 34 are amended to recite a particular 2'-modification, support for which can be found, for example, in parent application serial no. 08/465,866, at page 13, lines 29-34. No new matter has been added. Attached hereto is a marked-up version of the changes made to the claims by the present amendment. The attached page is captioned "Version with markings to show changes made."

As a preliminary matter, Applicants would like to direct the Examiner's attention to that the filing date accorded this application is incorrect. This application is a National Phase of International Patent Application Serial No. PCT/US98/08798, filed on April 30, 1998. Pursuant to Section 371, the filing date for this application is January 4, 2000, the date on which all of the requirements under that section were satisfied. The filing date presently accorded to this application is October 22, 1999. Applicants filed a petition with the Petitions Branch on July 16, 2002, to correct this issue.

Provisional Double Patenting

Claims 27, 28, 33 and 34 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 34 of copending Application no. 08/847,151. Also, claim 29 stands provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 34 of copending Application no. 08/847,151 in view of Milligan, *Journal of Medicinal Chemistry*, July 1993, Vol. 36, No. 14, pp. 1923-37) (“the Milligan reference”). Applicants reiterate that due to the provisional nature of the rejection, it will be addressed upon the indication of allowable subject matter in the present application and may be easily resolved by the filing of a terminal disclaimer at that time, if appropriate.

Rejections under 35 U.S.C. § 103

Claims 27-28, 33 and 34 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over any one of U.S. Patent No. 6,005,094 to Simon *et al.* (“the Simon patent”), U. S. Patent No. 5,792,615 to Arnold Jr, *et al.* (“the Arnold patent”), Agrawal *et al.*, *Biochem. Pharm.* 50 (4), pp. 571-576 (1995) (“the Agrawal reference”), taken separately and each further in view of Hanecak *et al.*, “Antisense Oligonucleotide Inhibition of Hepatitis C Virus Gene Expression in Transformed Hepatocytes”, *J. of Virology*, 1996, pp. 5203-12 (“the Hanecak reference”), Vlassov *et al.*, “Penetration of Oligonucleotides into Mouse Organism Through Mucosa and Skin”, *FEBS Letters* 327 (3), 1993, pp. 271-74 (“the Vlassov reference”); and Milligan *et al.*, *J. of Medicinal*

Chemistry, July 1993, Vol. 36, No. 14, pp. 1923-37 (“the Milligan reference”). Applicants do not concur.

“A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.” *In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000). “The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.” *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) (quoting *Interconnect Planning Corp. v. Feil*, 774 F. 2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985)). In order to establish a *prima facie* case of obviousness, “there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant.” *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). “In other words, the examiner must show reasons that the skilled artisan, confronted with the same problem as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.” *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1458 (Fed. Cir. 1998).

The Office Action asserts that the Simon and Arnold patents are directed to alimentary delivery of an oligonucleotide having a 2'-O-alkyl modification, and that 2'-O-alkyl includes 2'-methoxyethoxy groups. (*See* Office Action, page 3).¹ This is not correct. One skilled in the art

¹ Applicants note that in the Office Action dated August 28, 2001, the Examiner acknowledged that neither the Simon nor the Arnold patent discloses or suggests oligonucleotides comprising a 2'-alkoxyalkoxy modification

would *not* identify the species 2'-methoxyethoxy as belonging in the genus 2'-O-alkyl. The Simon and Arnold patents do not disclose or suggest a claimed invention, nor do they provide any motivation to modify teachings limited to 2'-O-alkyl modifications to produce a claimed invention. There is no evidence of record that one of ordinary skill in the art would be motivated to incorporate a $(\text{O-CH}_2\text{-CH}_2)_n\text{-O-alkyl}$ modification at the 2'-position in view of a discussion of a 2'-O-alkyl modification. These deficiencies are not remedied by the Agrawal and Hanecak references, as they are no longer available as prior art in view of Applicants' claim of priority.² Applicants respectfully submit that the deficiencies would not be remedied even if the references were still available for combination with the Simon and Arnold patents.

Furthermore, the Vlassov and Milligan references do not address the deficiencies noted in the Simon and Arnold patents. The Vlassov reference describes methods of alimentary delivery of an oligonucleotide with bioavailability and the Milligan reference discusses modified oligonucleotides comprising at least one nitrogenous heteroatomic backbone modification, including methylene(methylimino) linkages. Neither reference when combined with the Simon and Arnold patents produces a claimed invention, which is directed to alimentary deliver of an oligonucleotide comprising a 2'-modification comprising the formula $(\text{O-CH}_2\text{-CH}_2)_n\text{-O-alkyl}$. Indeed, there is no evidence of a motivation to modify the references to produce a claimed invention.

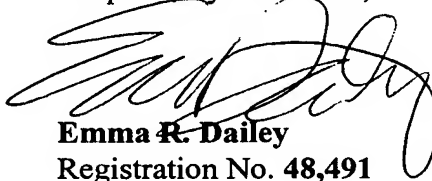
Applicants respectfully request reconsideration and withdrawal of the rejections as the Smith and Arnold patents, either taken independently or together with the Vlassov or Milligan references,

(e.g., 2'-methoxyethoxy modification or methylene(methylimino) (Office Action dated August 28, 2001, page 9, paragraph e).

do *not* teach or suggest the present inventions which are directed to alimentary delivery of an oligonucleotide comprising a $(\text{O}-\text{CH}_2-\text{CH}_2)_n$ -O-alkyl modification at the 2'-position. Furthermore, the cited references do not provide any motivation to modify the discussions therein to produce a claimed invention.

In view of the foregoing, Applicants submit that the claims presently before the Examiner are in condition for allowance. An Office Action to that effect is, therefore, earnestly solicited.

Respectfully submitted,



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2 The Agrawal reference was published in 1995 and the Hanecak reference was published in 1996, both of which are pre-dated by parent application serial no. 08/244,993, filed on June 21, 1994.

VERSION WITH MARKINGS TO SHOW CHANGES MADE**In the Specification**

On page 1, please amend the first paragraph as follows:

[This patent application is a National Phase application of International Patent Application serial no. PCT/US98/08798, filed on April 30, 1998, and is a continuation-in-part of application serial no. 08/847,151, filed on April 30, 1997.]

“Cross-Reference to Related Applications”

This patent application is a National Phase application of International Patent Application serial no. PCT/US98/08798, filed on April 30, 1998, and is a continuation-in-part of application serial no. 08/847,151, filed on April 30, 1997. This patent application is a continuation-in-part of application serial no. 08/465,866, filed on June 6, 1995, which is a continuation-in-part of application serial no. 08/244,993, filed on June 21, 1994, now U.S. Patent No. 5,623,065.

In the Claims:

Please cancel claim 33, without prejudice, and amend claims 27 and 34 as presented below:

27. (Amended) A method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising a [2'-O-alkoxyalkoxy modification] 2'-modification, wherein said 2'-modification comprises the formula

(O-CH₂-CH₂)_n-O-alkyl, and wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof.

34. (Amended) A method of modulating expression of a target nucleic acid comprising administering into the alimentary canal an effective amount of an oligonucleotide comprising a [2'-O-alkoxyalkoxy modification] 2'-modification, wherein said 2'-modification comprises the formula (O-CH₂-CH₂)_n-O-alkyl, and a heteroatomic backbone modification, wherein said oligonucleotide hybridizes to said target nucleic acid, and modulates the expression thereof.